

REMARKS

The undersigned appreciates the telephonic interview granted by the Examiners on October 4, 2005. The Interview Summary prepared by Examiner Clow has been reviewed and is believed to accurately set forth the content of the interview.

The specification has been amended to correct the cross-reference to the related provisional application. Equation (1) on page 10 has also been amended to correct a typographical error. Support for this change is found in claim 9 as filed and in equation (1) of the priority provisional application which has been incorporated by reference in the present application. A typographical error on page 1 has also been corrected.

New claims 65 and 66 have been added. Claims 1-22, 28-30, 33, 44, 46, 58, 60, 65 and 66 are presently pending in the present application. As a result of previous restriction requirements, claims 23-27, 31, 32, 34-43, 45, 47-57, 59, and 61-64 have been cancelled.

Claim Rejections under 35 U.S.C. §112

Claims 1-22, 28-30, 33, 44, 46, 58 and 60 are rejected under 35 USC 112, first paragraph as failing to comply with the written description requirement.

The claims have been amended to remove the expressions "or protein" and "or proteins" from the expressions "gene or protein" and "genes or proteins." As noted in the Interview Summary, it is believed that this new matter rejection will be withdrawn when all such limitations are removed.

Claim Rejections under 35 U.S.C. §101

Claims 1-22, 28-30, 33, 44, 46, 58 and 60 are rejected under 35 U.S.C. §101 on the ground that the claimed invention is directed to non-statutory subject matter.

All of the independent rejected claims have been amended to include "providing a list of genes whose associated values differ by an amount of statistical significance among the sets." Support for this limitation can be found throughout the specification, but especially on page 14, lines 3-11, page 16, line 32 to page 18, line 5 and Appendix B. As noted in Table 2 of Appendix B, the Table contains a list of genes with changes in expression called significant by SAM, which is one embodiment of the invention. As amended, in the preamble of all of the rejected independent claims, the associated values of the genes comprise "levels of mRNA or protein."

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Support for such limitation can be found in the specification, on page 4, lines 1-4 and page 9, lines 17-18.

Claims 1, 44 and 58 have also been amended to clarify that variables related to the parameters are adjusted so that they are substantially independent of variations in scatter values or average associated values of the genes over the sets. Support for this amendment can be found on page 11, lines 28-33.

As so amended, the rejected independent claims are believed to clearly set forth a process that causes a physical transformation outside the computer for which a practical application in the technical arts is disclosed in the specification. Thus the parameters that are processed in the various claim elements of the rejected claims relate to behavior of genes in the real physical world and are not mere abstractions. Hence the various claim elements of the rejected independent claims are believed to recite physical processes that result in physical transformation outside the computer.

Furthermore, as noted by the Court of Appeals of the Federal Circuit in the case of *Arrhythmia Research Technology, Inc. v. Corazonix Corp.*, 22 U.S.P.Q. 2d, 1033 at 1038, referring to claim 1 (a method claim) of U.S. Patent 4,422,459, "these claimed steps of . . . and 'comparing' are physical process steps that transform one physical, electrical signal into another. The view that 'there is nothing necessarily physical about 'signals'' is incorrect." The Federal Circuit then quoted in re Taner, 214 U.S.P.Q. 678, 681 (CCPA 1982) with approval, where the court held that a method of seismic exploration including the mathematically described steps of "summing" and "simulating from" is statutory. Therefore the claim element "comparing the observed and expected values of the parameter to identify genes whose associated values differ by an amount of statistical significance among the sets" in all of the rejected independent claims is a physical process that results in physical transformation outside the computer under the court holdings in these two cases, and under MPEP 2106, and renders these claims statutory.

From the above, all of the rejected independent claims are now believed to recite statutory subject matter.

All of the independent rejected claims have been amended to include "providing a list of genes whose associated values differ by an amount of statistical significance among the sets." New claims 65 and 66 contain the element of "identifying from the plurality of genes those

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whose associated values differ by an amount of statistical significance among the sets.” These claims are now believed to comply with the utility requirement under 35 U.S.C. 101.

Claim Rejections under 35 U.S.C. §102

Claims 1-7, 16, 17, 28, 44, 58 and 60 are rejected under 35 U.S.C. §102(a) and 102(e) as being anticipated by Scherer, WO 99/58720. The rejection is respectfully traversed insofar as it is applied to the claims as amended.

Claims 1, 44 and 58 have been amended to require that the scatter values be defined by standard deviation of the associated values in the sets. This clearly differentiates claims 1, 44 and 58 from Scherer. Thus, the parameters of the plurality of genes are adjusted so that variables related to the parameters are substantially independent of variations in scatter values or average associated values of the genes where the scatter values are defined by the standard deviation of the associated values in the sets. This is radically different from Scherer. Scherer discloses on pages 23-27 nothing more than a process for controlling background noise and normalization. Such process has nothing to do with the above-described feature of claims 1, 44 and 58 and does not teach or suggest such a feature.

Scherer describes a comparison of replicate gene expression profiles having a normal distribution about zero due to random measurement errors. Scherer uses the standard deviation of the distribution as a guide for setting an empirical threshold. Page 39, lines 7-15. This threshold is then used for identifying genes of statistical significance. In contrast, for claims 1, 44 and 58, genes whose associated values differ by an amount of statistical significance among the sets are identified by comparing the observed and expected values of the adjusted parameter for each gene from the sets of associated values. Moreover, in one implementation of the invention in these claims, the expected values are derived by a process involving permutation of the associated values; no thresholds are directly set using the standard deviation. Please see page 12, line 29 through page 14, line 11 of the specification, including equation (3). Scherer therefore actually teaches away from the above-described features of claims 1, 44 and 58.

In view of the above, claims 1, 44 and 58 are believed to be allowable. Claims 2-7, 16, 17 are also believed to be allowable since they depend from allowable claim 1; they are further believed to be allowable on account of the limitations of these claims. Thus claim 2 adds the limitation that the adjusting includes dividing the scattered values or average associated values of

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the genes into subsets each having a similar range of values, and calculating the standard deviation of each of the parameters within each subset. The parameters are then altered until a coefficient of variation of the standard deviations of the parameters among the subsets is minimized. Page 30, lines 11-23 of Scherer relied on by the Examiner fails to teach or suggest such features in claim 2. Such section of Scherer discusses nothing more than the fact that the mean gene expression signal may not be constant when only a small percentage of a cell's expressed genes is assessed, so that the normalization process (dividing each signal by the sum of all signals) may be omitted when a small subset of genes is chosen. Such disclosure fails to teach or suggest the above-described features of claim 2 and the Examiner has failed to explain why it would. The mean gene expression of Scherer appears to be entirely different and distinct from these features of claim 2.

In claim 7, the parameter is defined to be a function of the scatter value and of the difference value. Given the definition of scatter value (standard deviation of the associated values in the sets) in claim 1, such feature is also not taught or suggested by Scherer.

While Scherer discusses the variability of data, on pages 27-30, the description on these pages contains nothing more than a very general description of such variability. The solution produced by Scherer is normalization with the mean signal, across all genes, which signal is assumed to be constant. Normalization is achieved by dividing each signal by the sum of all signals. Page 30, lines 7-10. Such process is very different from those of claims 16 and 17 and do not teach or suggest such features. Thus, in claim 16, the parameter is selected using a quantity related to variances between the associated values in the subsets of the sets and the variances of the associated values within each subset of the sets. In claim 17, the quantity of claim 16 relates to the sum of variances between the associated values in the subsets of the sets and the sum of variances of the associated values within each subset of the sets.

While the Examiner rejected claims 28 and 60 in view of Scherer, the Examiner has failed to articulate why these claims are anticipated by Scherer and thus failed to provide the proper basis for the rejection. Therefore, if the Examiner maintains the rejection, it is respectfully requested that the Examiner provide the reasoning for the rejection, and the next Office Action should not be made final so as to permit Applicant a chance to respond to such rejection and/or amend claims if desired without restriction. Since the Examiner has failed to set forth the grounds of rejection, the applicant is deprived of the opportunity to respond to them in

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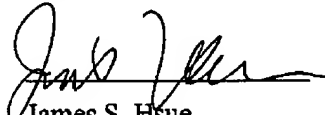
this Amendment. Nevertheless, it is noted that Scherer has failed to teach or suggest the feature in these claims that the values of the parameter of the genes be ranked and that an expected value of such parameter for each rank be provided. Scherer also fails to teach or suggest permuting the associated values in the original sets to arrive at sets different from the original sets for each permutation, deriving a value of such parameter for each permutation and then ranking such values. The calculated and expected values for the parameter of the same rank are then compared to identify genes whose associated values differ by an amount of statistical significance among the sets. Scherer fails to teach or suggest such features.

New claims 65 and 66 have been added to more completely cover the invention. These two claims are also believed to be allowable.

CONCLUSION

In view of the amendments and remarks contained herein, it is believed that all claims are in condition for allowance and an indication of their allowance is requested. However, if the Examiner is aware of any additional matters that should be discussed, a call to the undersigned attorney at: (415) 318-1162 would be appreciated.

Respectfully submitted,


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